European Patent Office
Erhardtstraße 27
D-80298 München 2
Germany

Re: Opposition proceedings
concerning EP-B-0125023
of Genentech, Inc. *et al.*

DECLARATION OF LEON R. LYLE, Ph.D.

I, Leon R. Lyle, Ph.D. declare and say as follows: -

1. I have received B.A. and M.A. degrees in Biology and Microbiology from Drake University, Des Moines, Iowa, U.S.A. and a Ph.D. in Microbiology from Montana State University, Bozeman, Montana, U.S.A., and hold the position of Director, Technology Planning at Mallinckrodt Medical, Inc., St. Louis, Missouri, U.S.A. My Curriculum Vitae is attached hereto as Exhibit "A" and forms part of this Declaration.

2. I have no association whatsoever with Genentech, Inc., South San Francisco, California (other than as custodian of a few Genentech shares under the Uniform Gift to Minors Act), or the City of Hope, Duarte, California, which, I was informed, are the joint owners of the above-identified European patent.

3. I attended the Ninth Annual Meeting of the Clinical Ligand Assay Society which was held on March 13-17, 1983 in the Franklin Plaza Hotel, Philadelphia, U.S.A. The meeting had about 200-250 participants, and the oral and poster presentations embraced a variety of topics from the fields of analytical and diagnostic assays and antibody technology. The meeting, just as other meetings of the Clinical Ligand Assay Society, was not followed by the publication of a conference book or proceedings. At the time of the meeting the organizers provided the participants with a Syllabus, which contained those presentations by invited

speakers and those abstracts which had been submitted sufficiently in advance of the meeting for their printing, binding, and shipment to have taken place.

4. In and around 1983 I was actively involved in research pertaining to the production of monoclonal antibodies by hybridoma technology. At a breakfast roundtable of the 1983 Ligand Assay Society meeting I delivered a short presentation entitled "Practical Problems in the Production of Monoclonal Antibodies" with the declared purpose of facilitating the exchange of non-proprietary information among people responsible for the operation of hybridoma laboratories. A copy of the Abstract of this presentation along with the front pages and the author's index of the Syllabus of the Ninth Annual Meeting, in which it was published, is attached as Exhibit "B".

5. Because I had, and still have, a keen interest in antibody technology, I remember that the recipients of the 1983 Award (sponsored by Mallinckrodt, Inc., my employer) were Dr. Köhler and Dr. Milstein, who were first to develop the hybridoma method for the production of monoclonal antibodies. I remember that, to my disappointment if not necessarily to my surprise, both Dr. Köhler and Dr. Milstein were unable to attend the meeting. Instead, Dr. Marc Shulman accepted the Award and delivered the Mallinckrodt Award Lecture on their behalf. No written record was made available with respect to Marc Shulman's lecture at or after the meeting, including the Syllabus. This is apparent from the author's index submitted as part of Exhibit "B", which does not include Dr. Shulman's name. Therefore, there is nothing on which one can rely except one's own recollection or notes as to the content of Dr. Shulman's lecture.

6. It is my recollection that in his lecture, Dr. Shulman provided an overview of monoclonal antibodies and monoclonal antibody technology. Nothing in Dr. Shulman's lecture struck me as new revelations. I remember the lecture as being of general, review-type nature, which did not contain information that would have exceeded public knowledge at the time. I do not recall any

discussion of methods of recombinant DNA technology for the production of antibodies. I do not recall any discussion of chimeric antibodies or chimeric antibody technology. Specifically, I have absolutely no recollection of any mention of the replacement of an immunoglobulin gamma chain constant region by another constant region to alter the immunoglobulin's cytolytic activity, although the effector functions of the different subclasses of mouse IgG's may have been discussed. I have no recollection whatsoever of any discussion of substituting the constant region of a human antibody for the constant region of a mouse antibody to produce an immunoglobulin molecule which would be superior in human therapy.

7. I declare that the foregoing is true and correct to the best of my information and belief, and that this declaration was executed on this 9th day of August, 1994, St. Louis, Missouri.

Leon R. Lyle

Leon R. Lyle, Ph.D.
Director, Technology Planning

Ex A

CURRICULUM VITAE

NAME:	Leon R. Lyle
SOCIAL SECURITY NUMBER:	480-48-1714
AGE (Date of Birth):	52 (11/28/41)
PLACE OF BIRTH:	Ottumwa, Iowa (USA)
MARITAL STATUS:	Married
Spouse:	Mary Jane Lyle Assistant U.S. Attorney US Attorney's Office - St. Louis
Children:	Elizabeth, age 17 Dan, age 14
OFFICE:	Mallinckrodt Medical, Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, Missouri 63134 (314) 895-2352 (314) 895-8992 (FAX)
HOME:	1319 Webster Path Drive Webster Groves, Missouri 63119 (314) 968-8029

EDUCATION:

1963 B.A.	Biology, Drake University, Des Moines, Iowa
1967 M.A.	Microbiology, Drake University Des Moines, Iowa
1969 Ph.D.	Immunology and Microbiology Montana State University Bozeman, Montana

1970-1973	NIAID Post-Doctoral Fellow Washington University School of Medicine St. Louis, Missouri Cellular Immunology. Research dealt with mechanisms of antigen recognition and lymphocyte transformation, Immunology Department, Dr. Charles W. Parker

HONORS:

1968	Received Montana State University Institutional Phi Sigma Award for "Outstanding Achievement as a Graduate Student."
1969	Sigma Xi - elected to Associate Membership
1981	President's Award for Technical Innovation, Mallinckrodt, Inc.

MEMBERSHIPS:

American Association of Immunologists
American Society for Microbiology
American Association for Clinical Chemistry
American Association for the Advancement of Science
Association of University Technology Managers
Society of Nuclear Medicine

WORK EXPERIENCE:

1991- Current — Director, Technology Planning

Responsible for the identification and development of new technical and business opportunities in Radiology, Cardiology, Nuclear Medicine, Oncology, Anesthesiology and Critical Care. Development and Administration of Mallinckrodt Medical's extramural research programs with universities. Primary personal technical focus is on chemoattractant cytokines involved in inflammation.

1985 - 1991 — Associate Director, Immunoassay R&D, Mallinckrodt, Inc.

Responsible for the Hybridoma Sciences Section and R&D, Europe on a technical/functional basis. Overall responsibility for R&D activities in in vitro diagnostics in U.S. and Europe. Responsible for coordination with Japan In Vitro R&D. Experienced also in regulatory matters concerning in vitro immunodiagnostics for both human and veterinary applications.

1984 - 1985 — Assistant Director, Hybridoma Sciences R&D, Mallinckrodt, Inc.

Responsible for management of the Hybridoma Section, general cell culture, monoclonal antibody based assay development efforts and coordination with two other International R&D facilities in in vitro diagnostics. Group has developed numerous high affinity antibodies which are being utilized in commercial products in Europe and Japan.

1982-1984 Research Manager, Hybridoma Sciences R&D, Mallinckrodt, Inc.

In 1982, I requested the assignment of further accelerating the hybridoma program. Developed capital projects for additional laboratory space and strategic plan. Recruited and trained personnel. Group was very efficient and produced high quality monoclonal antibodies to numerous analytes. Group responsible for support of production and International R&D projects. Also responsible for liaison function with and monitoring progress of a large cooperative hybridoma effort with a local medical school. Developed R&D, marketing, and advertising strategy for the antibodies coming from the program and implemented. All products marketed on schedule. This project was cited by management as an "example of perfect project execution".

1980-1982 Assistant Director, Immunoassay Section, Mallinckrodt, Inc.

Overall responsibility for the Department, 5 Ph.D.'s and 13 staff scientists. Responsible for new product planning, budget, general administration, safety and GLP compliance. Responsible for product improvement, production transfer and production trouble shooting. Group developed improved βhCG test which was very favorably reviewed in the clinical literature. Initiated microbiology program. Led the project team responsible for the introduction of Dirotect™, the first USDA licensed ELISA test for dog heartworm. Early in 1980, was given the responsibility of bringing hybridoma technology into the Company. This was accomplished. Developed high affinity monoclonal antibodies to T4 which were utilized in the SPAC™ solid support system and in a free T4 test currently marketed in Europe.

1975-1980	Group Leader, Mallinckrodt, Inc. Supervised 2 Ph.D.'s and 4 staff scientists in product development. Group developed RIA-QuantTM hCG assay, and a liquid hTSH assay. Personally handled development of iodination procedures for these materials and design of stability studies used by the Department. Assisted in preparation of 510k submissions. Group also developed RIA-Mat™ T4 and T3 tests. These products were converted to lyophilized products and then to solid support tests, the SPAC™, Digoxin, T3, T4 and T3U (uptake). Group also developed Folate and B12 tests (not marketed).
1973-1975	Radiopharmaceutical Chemist, Mallinckrodt, Inc. Primary responsibilities involved product development and transfer to operations. Developed RIA-Mat™ Digoxin test.

APPOINTMENTS:

1981-1984	Immunology Devices Advisory Panel Office of Medical Devices, FDA (Industrial Representative)
1984-1988	(Reappointed) Term ended February 29, 1988
1987	Scientific Program Chairman Clinical Ligand Assay Society National Meeting St. Louis, Missouri

SELECTED
BIBLIOGRAPHY:

Lyle, L.R. and Parker, C.W., "Cyclic adenosine 3',5'-monophosphate response to oncanavalin A in human lymphocytes. Evidence that the response involves specific carbohydrate receptors on the cell surface," Biochemistry 13: 5415-5420 (1974).

Lyle, L.R. and Parker, C.W., "New approaches to immunosuppression," Fed. Proc. 33: 1889-1893 (1974).

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Scott, M.G., W.H. Lin, L.R. Lyle, P.R. Atkinson, J.E. Seeley and E. Markoff. Monoclonal Antibodies Specific For Non-Glycosylated Porcine Prolactin and for Pituitary Porcine Prolactin. B&BRC, 151, 1427-1433 (1988).

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Miller, K.M., J.H. Wilbe, J.R. Coveney, L.R. Lyle, P.E. Gargan, V.A. Ploplis and A.R. Fritzberg. Imaging Thrombin in a Rabbit Jugular Vein with Technetium-99M Mlt-1 Monoclonal Antibody. J. Nuc. Med. 31: 747 (1990), Also, J Labelled Compd Radiopharm 30: 322 (1991), Fibrinolysis 4: 39 (1990), K.M. Miller and L.R. Lyle USP 5,080,883 January 14, 1992.

Barnhart, J.L., M. Harada, L.R. Lyle and C.A. Savaris. Immunologic Reactions of Human Recipients to Repeated Exposures to Albunex Microspheres, Investigative Radiology 26: S198-200 (1991).

Majacha, R.E., J.M. Reno, R.P. Friedland, C. Vanhaight, L.R. Lyle and C.A. Marotta. Development of a Monoclonal Antibody Specific for Beta-A4 Amyloid in Alzheimer's Disease Brain for Application to In-Vivo Imaging of Amyloid Angiopathy. J. Nucl. Med. 33: 2184-2189 (1992). Also, Neurology 41: 156 (1991), J. Cerebral Blood Flow and Metabolism 11: S186 (1991).

Hay, R.V., R.S. Skinner, O.C. Newman, S.L. Kunkel, L.R. Lyle, B. Shapiro and M.D. Gross. Nuclear Imaging of Acute Inflammatory Lesions with Recombinant Human Interleukin-8. Presented, Soc. Nuc. Med. Meeting June 11, 1993.

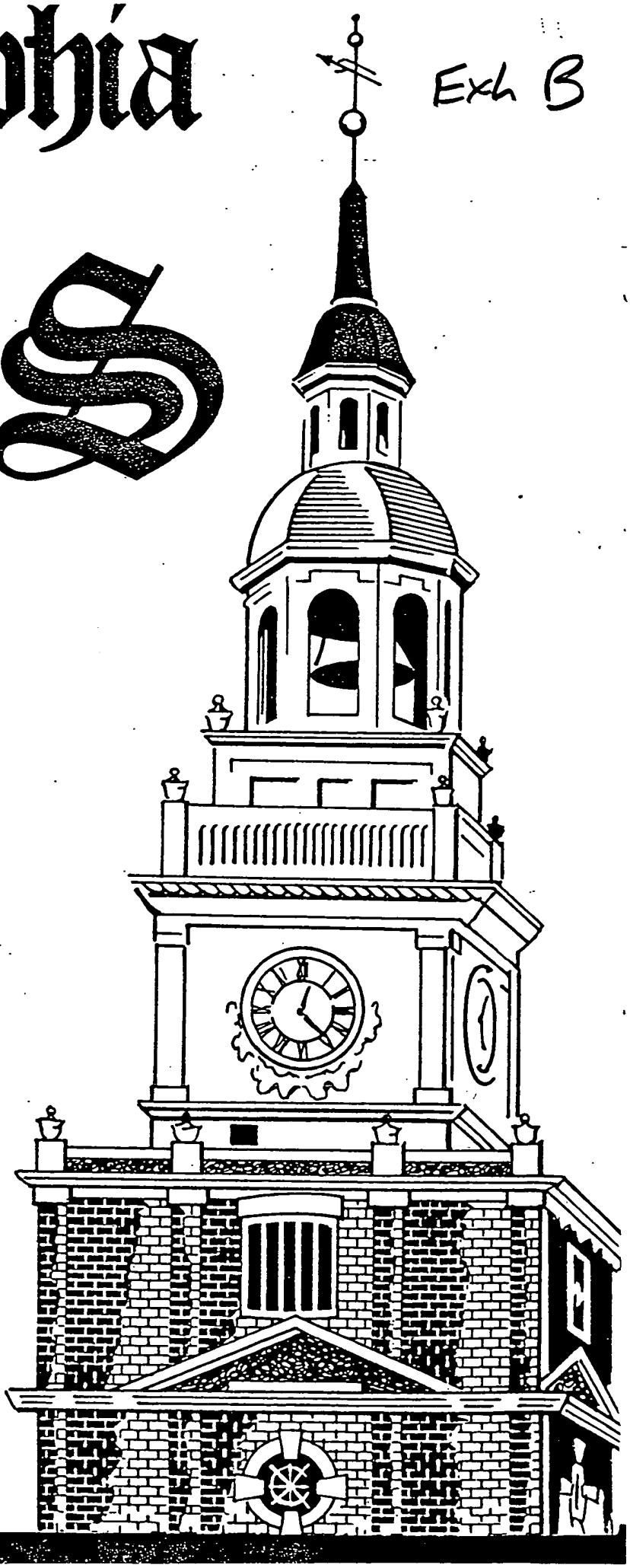
Philadelphia

Exh B

celebrates

CLAS

SYLLABUS



inth Annual
leeting & Exhibit
anklin Plaza Hotel
hiladelphia, PA
larch 13-17, 1983

PRACTICAL PROBLEMS IN THE PRODUCTION OF MONOCLONAL ANTIBODIES, Leon Lyle, Ph.D., Mallinckrodt Diagnostics, St. Louis, MO

The objective of the meeting is to provide a forum for the exchange of non-proprietary information among people responsible for the operation of hybridoma laboratories. The discussion will address technical issues, problems and their resolution, and day-to-day laboratory operations. The topics will include: laboratory planning and start-up, fine points of technique, high volume antibody production and Regulatory considerations.

The goal is that the participants will exchange information on these points indicating what methods work best for them, specific problems they have encountered, how they dealt with them and what steps they have taken to prevent reoccurrence. Participants should be willing to act as resources to one another, both for these and subsequent discussions.

SYLLABUS

NINTH ANNUAL MEETING

CLINICAL LIGAND ASSAY SOCIETY

MARCH 13-17, 1983

PHILADELPHIA, PENNSYLVANIA

Barry J. Burns, Ph.D.

SYLLABUS EDITOR

Available from:

Clinical Ligand Assay Society, Inc.
P.O. Box 67
Wayne, MI 48184
313-722-6290

Foreword

Traditionally, the Annual Meeting Syllabus contains the presentations by invited speakers and workshop faculty as well as the submitted abstracts, and is made available at the time of the meeting. This objective annually presents a challenge to the Syllabus Editor in terms of obtaining the articles sufficiently in advance of the meeting so that printing, binding, and shipment can be achieved. This year has proved to be no exception, especially since the meeting this year is almost two months earlier than it has been in the past.

Several of our invited speakers were unable to submit manuscripts within our time constraints due to their own heavy work schedules. Nevertheless, the volume contains excellent papers from the majority of our invited speakers, and we believe this year's Syllabus is a worthwhile reference book. The Editor appreciated the fine effort of the invited speakers who did submit manuscripts in meeting the extraordinary time limitations asked of them.

In addition the Editor acknowledges the extra effort made by all committee members in bringing about this fine well rounded program in so short a period of time.

Barry J. Burns

European Patent Office
Erhardstrasse 27
D-80331 Munich
Germany

Subject:	Opposition to European Patent EP 1 120 694 B1 Appl. No.: 84 301 996.9
Patent Owner:	Celltech Limited 244-250 Bath Road Slough, Berkshire, SL1 4DY (GB)
Title:	PROCESSES FOR THE PRODUCTION OF MULTICHAIN POLYPEPTIDES OR PROTEINS

- and -

Subject:	Opposition to European Patent EP 0 125 023 B1 Appl. No.: 84 302 368.0
Patent Owner:	Genentech, Inc. South San Francisco, California United States of America
Title:	RECOMBINANT IMMUNOGLOBULIN PREPARATIONS, METHODS FOR THEIR PREPARATION, DNA SEQUENCES, EXPRESSION VECTORS AND RECOMBINANT HOST CELLS THEREFOR

DECLARATION OF MARC J. SHULMAN

I, MARC J. SHULMAN, hereby declare:

1. I am a Professor of Immunology and Molecular and Medical Genetics in the Faculty of Medicine, Medical Sciences Building, University of Toronto, Toronto, Ontario, Canada, M5S 1A8.

2. I began conducting research in the immunoglobulin (Ig) field in the mid 1970's at the Basel Institute for Immunology. While there, I worked primarily with Dr.

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